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Running title: $PM_{2.5}$ air pollution and mortality in a US cohort

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Abstract

Background: Outdoor fine particulate matter ($PM_{2.5}$) has been identified as a global health threat, but the number of large U.S. prospective cohort studies with individual participant data remains limited, especially at lower recent exposures.

Objectives: To test the relationship between long-term exposure $PM_{2.5}$ and death risk from all non-accidental causes, cardiovascular (CVD), and respiratory diseases in 517,041 men and women enrolled in the National Institutes of Health-AARP cohort.

Methods: Individual participant data were linked with residence $PM_{2.5}$ exposure estimates across the continental U.S for a 2000-2009 follow up period when matching census-tract level $PM_{2.5}$ exposure data were available. Participants enrolled ranged from 50-71 yrs. of age, residing in 6 U.S. States and 2 cities. Cox Proportional Hazard models yielded Hazard Ratio (HR) estimates per 10 $\mu g/m^3$ of $PM_{2.5}$ exposure.

Results: $PM_{2.5}$ exposure was significantly associated with total mortality (HR= 1.03, 95% CI =1.00, 1.05) and CVD mortality (HR=1.10, 95% CI=1.05, 1.15), but the association with respiratory mortality was not statistically significant (HR=1.05, 95% CI=0.98,1.13). A significant association was found with respiratory mortality only among never smokers (HR=1.27; 95% CI: 1.03, 1.56). Associations with 10 $\mu g/m^3$ $PM_{2.5}$ exposures in yearly participant residential annual mean, or in metropolitan area-wide mean, were consistent with baseline exposure model results. Associations with $PM_{2.5}$ were similar when adjusted for ozone exposures. Analyses of California residents alone also yielded statistically significant $PM_{2.5}$ mortality HR's for total and CVD mortality.

Conclusions: Long-term exposure to $PM_{2.5}$ air pollution was associated with an increased risk of total and CVD mortality, providing an independent test of the $PM_{2.5}$ – mortality relationship in a new large U.S. prospective cohort experiencing lower post-2000 $PM_{2.5}$ exposure levels.

Introduction

Over the past several decades, numerous published epidemiologic studies have documented a consistent association between long-term exposure to fine particulate matter mass ($PM_{2.5}$) air pollution and an increase in the risk of mortality around the globe (e.g., Beelen et al. 2014; Brook et al. 2010; Crouse et al. 2012; Dockery et al.1993; Eftim et al. 2008; Ostro et al. 2011; Ozkaynak and Thurston 1987; Pope et al. 1995; Pope et al. 2002; Pope et al. 2004). Pope and collaborators notably found elevated relative risks of cardiovascular (CVD) mortality in association with long-term $PM_{2.5}$ exposure [hazard ratio (HR) per 10 $\mu g/m^3$ = 1.12; 95% CI=1.08, 1.15] in the largest and most definitive U.S. nationwide cohort considered to date (Pope et al. 2002, 2004), providing a cardiovascular mortality hazard ratio (HR)=1.12 per 10 $\mu g/m^3$ (95% CI=1.08,1.15). However, existing US cohort studies of $PM_{2.5}$ health effects are still being questioned (e.g., Reis 2013). In addition, particulate matter air pollution levels have been declining in recent years in the US, so there is a need to confirm whether studies conducted in the past at higher levels are replicable today. Thus, it is important to test these associations in another large U.S. cohort with detailed individual-level risk factor information on participants, especially one for which pollution exposures can be estimated at the individual participant residence level, and in more recent lower $PM_{2.5}$ exposure years, as we report here. This research addresses these needs using the newly available U.S. National Institutes of Health AARP Diet & Health cohort (NIH-AARP Study) (Schatzkin et al. 2001).

Methods

Study Population.

The NIH-AARP Study was initiated when members of the AARP, aged 50 to 71 years from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania)

and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan), responded to a mailed questionnaire in 1995 and 1996. Details of the NIH-AARP Study have been described previously (Schatzkin et al. 2001). Among 566,398 participants enrolled in the NIH-AARP cohort and available for analysis in 2014, we first excluded for this analysis those individuals: for whom the forms were filled out by a proxy (15,760, or 2.8%); who moved out of their study region prior to January, 2000 (13,863, or 2.4%); who died prior to January 1, 2000 (21,415, or 3.8%), and; those for whom census-level outdoor $PM_{2.5}$ exposure was not estimable using the methods discussed below (737, or 0.1%). After accounting for overlapping exclusions, the analytic cohort includes 517,041 (91.3%) participants for whom matching $PM_{2.5}$ air pollution data were available. The NIH-AARP cohort questionnaires elicited information on demographic and anthropometric characteristics, dietary intake, and numerous health-related variables (e.g., marital status, body mass index, education, race, smoking status, physical activity, and alcohol consumption) at enrollment only. Contextual environment characteristics (e.g., median income) for the census tract of each of this cohort's participants have also been compiled for this population by the NIH-AARP Study (NIH-AARP, 2006), allowing us to also incorporate contextual socio-economic variables at the census-tract level. All participants provided informed consent prior to completing the study questionnaire. The study was approved by the Institutional Review Boards of the National Cancer Institute and New York University School of Medicine.

Cohort Follow-up and Mortality Ascertainment.

Vital status was ascertained through a periodic linkage of the cohort to the Social Security Administration Death Master File and follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings. Participants were

followed for address changes using the U.S. Postal Service's National Change of Address database, responses to other study-related mailings such as newsletters, and directly from cohort members' notifications (Michaud et al., 2005). We used the *International Classification of Diseases, Ninth Revision* and the *International Statistical Classification of Diseases, 10th Revision* to define death due to cardiovascular disease (CVD) (ICD 10: I00-I99), non-malignant respiratory disease (ICD 10: J00-J99), and deaths from non-external and non-accidental deaths (ICD-10 A00-R99). During the follow-up period considered here (2000 through 2009), 86,864 (16.8%) participants died, of which 84,404 (97.2% of deaths) participants died of non-external and non-accidental causes.

Air Pollution Exposure Assessment.

Outdoor annual $PM_{2.5}$-related exposures at the census-tract level for residences at NIH-AARP cohort entry were estimated using data from the U.S. EPA's nationwide Air Quality System (AQS, formerly AIRS) (http://www.epa.gov/airdata/). The nationwide AQS Network includes nearly 3000 sites, has operated since the 1970's, and has included measurement of $PM_{2.5}$ mass since mid-1999. The year 2000 was selected as the start of follow-up in this study because that is the first full year that outdoor $PM_{2.5}$ exposure data were available nationwide. The contiguous U.S. map in Figure 1 displays the census tracts in which the members of this cohort resided at the start of the study. Private residence locations were not included in the original NIH-AARP Cohort dataset in order to protect participant privacy. As a result, we employed census tract centroid estimates of monthly average $PM_{2.5}$ mass exposures available through the year 2008, as obtained from a published hybrid land use regression (LUR) geo-statistical model (Beckerman et al., 2013), and as matched with individuals by NIH to further protect participant anonymity. Exposure was considered only through 2008 because the time dependent model

matched deaths with exposure in each prior year, and follow-up ended in 2009 for these analyses. These estimates used ambient AQS $PM_{2.5}$ as the dependent variable and traffic and land use information as predictors (Beckerman et al. 2013). Residuals from this model were interpolated with a Bayesian Maximum Entropy (BME) model, and the estimates from the LUR and BME were combined post hoc to derive monthly estimates of $PM_{2.5}$. To allow investigation of possible confounding by O_3 exposure, annual Primary Metropolitan Statistical Area (PMSA) mean ozone (O_3) exposures were also estimated for the year 2000 by averaging annual O_3 means from all ambient monitoring sites with >75% of possible days of data in each PMSA (including 391 sites among 93 PMSA's) (USEPA, 2014). The PMSA mean $PM_{2.5}$ mass concentrations in 2008, at the end of the exposure period, were lower than, but highly correlated with their paired PMSA mean concentration in 2000 ($R^2 = 0.77$), suggesting that the spatial rank ordering of $PM_{2.5}$ concentrations remained consistent over the follow-up period. However, the number of cohort participants living below the U.S. annual $PM_{2.5}$ standard (12 $\mu g/m^3$) increased over time, rising steadily from only 33% of cohort participants in 2000 (mean = 13.6 $\mu g/m^3$, SD = 3.6) up to 78% of cohort participants living below the 12 $\mu g/m^3$ annual $PM_{2.5}$ standard in 2008 (mean = 10.2 $\mu g/m^3$, SD = 2.3). Therefore, to incorporate these exposure level changes over the follow-up time, we also developed annual mean exposures at the census tract centroid of each participant's residence at baseline to incorporate into a time-dependent sensitivity analysis of the $PM_{2.5}$ - mortality association, with censoring for those known to have moved.

Statistical Methods.

Person years of follow-up were included for each participant from January 1, 2000 to the date of death, the end of follow up (December 31, 2009), or the date the participant moved out of the State or city where they lived at enrollment, whichever occurred first. This period was

selected because that is the time period for which outdoor $PM_{2.5}$ exposure estimates were available nationwide at the census-tract level for matching with the cohort mortality data (Beckerman et al. 2013). For the time-independent exposure model, the exposure metric was each participants's annual mean enrollment census tract centroid $PM_{2.5}$ exposure in the first year of this mortality analysis, 2000, which was the first complete year of $PM_{2.5}$ data availability across the US. In addition, we also considered a time-dependent (annual mean) model, for which annual mean census-tract level exposure to $PM_{2.5}$ was treated as time-varying, with a one-year lag. For example, mortality risk during 2000 was related to each participant's enrollment residence census tract-specific average $PM_{2.5}$ for 1999.

We used the Cox proportional hazards models (Cox and Oakes 1984; Fleming and Harrington 1991) to estimate relative risks (RRs) of mortality and 95% confidence intervals (CIs) in relation to ambient $PM_{2.5}$ (per 10 $\mu g/m^3$). In multivariate models including individual-level variables, we treated age (in 3 year groupings), sex and region (6 US States and 2 municipalities of residence at study entry) as strata and adjusted for the following individual covariates and potential risk factors at enrollment: race (non-hispanic white, non-hispanic black, other), education (less than 8 years, 8-11 y, high school, some college, college graduate), marital status (married, never-married, or other, including widowed/divorced/separated and unknown), Body Mass Index (<18.5 kg/m^2, 18.5-<25.0, 25.0-<30.0, and 30-<35, 35+ kg/m^2), alcohol consumption (none, <1, 1-2, 2-5 and 5+ drinks per day), and smoking history (never smoker, former smoker who quit at least one years ago of <= 1 pack/d, former smoker who quit at least one years ago of >1 pack/d, quit less than year ago or current smoker of <= 1 pack/d, quit less than a year ago or current smoker of >1 pack/d). We also included two contextual characteristics of the participants' residential census tracts found to modify The $PM_{2.5}$-mortality HR estimates

and have statistical significance in our analyses (data not shown): (1) median census tract household income; and (2) % of census tract population with less than a high school education, based on the 2000 decennial census for the residence at study entry, as included in the cohort dataset (NIH-AARP, 2006). Potential effect modification was assessed by including multiplicative interaction terms between $PM_{2.5}$ concentrations and each covariate [e.g., sex, age <65 or ≥65 years, age and sex combined, education (< high school, high school, >high school) and smoking (never, former, current) at baseline] in the proportional hazards models. Likelihood ratio statistic p-values (two-sided) comparing model fit with and without interaction terms were used to test the statistical significance of each interaction, with p-values of <0.05 defined as statistically significant. Statistical analyses were carried out in SAS (version 9.3) and R (version 3.0.1), using the "survival" package (RDCT, 2009).

Additional sensitivity analyses were conducted, including: models without adjusting for contextual variables; limiting the analysis to California residents; without censoring data after people moved; adjusting for ozone, and using $PM_{2.5}$ exposures estimated at the metropolitan area average level (rather than at the Census tract level). In addition, other contextual characteristics were also considered: (1) Gini coefficient, a metric of income inequality; (2) % of census tract population that are black; (3) % of census tract population that are unemployed; and, (4) % of census tract population living below the poverty level, but were not included in the final model, as addition of these variables did not significantly affect results. To allow more direct comparisons with past work applying random effects methods (e.g., Krewski et al. 2009), we also evaluated HRs in relation to baseline (2000) $PM_{2.5}$ exposure levels while incorporating random effects for State of residence using the "coxme" package in R.

In order to show how the shape of the $PM_{2.5}$–mortality relationship response varies with concentration in this cohort, $PM_{2.5}$ natural spline (ns) plots with 4 df were prepared for both total (all cause) and cardiovascular mortality using standard Cox models for the baseline case, stratified by age and sex, and adjusted for all individual-level covariates and contextual variables, as described above.

Results

The cohort was exposed to a wide range of $PM_{2.5}$ concentrations (Table 1), with a concentration range similar to the nation as a whole (U.S. EPA 2009). With the exception of race (for which Table 1 indicates a rising exposure with increasing percentage of Black participants), cohort characteristics were generally similar across $PM_{2.5}$ exposure level, limiting the potential for confounding in our $PM_{2.5}$ mortality relationship analyses.

In our time-independent baseline exposure Cox model analyses of the selected cohort (using the study entry tract of residence $PM_{2.5}$ mean as the exposure reference for each participant), higher levels of ambient $PM_{2.5}$ exposure were significantly associated with increased mortality due to all causes of (non-accidental) death (HR = 1.03 per 10 $\mu g/m^3$ $PM_{2.5}$; 95% CI 1.00, 1.05) and cardiovascular disease (HR 1.10; 95% CI 1.05, 1.15), as presented in Table 2. Stratified analyses by sex, age, and education for this cohort did not indicate significant differences in $PM_{2.5}$ effect estimates across categories (Table 2). However, while $PM_{2.5}$ exposure was not significantly associated overall with increased risk of respiratory mortality (HR=1.05; 95% CI: 0.98,1.13), an association was found for never smokers (HR=1.27; 95% CI: 1.03,1.56). Figure 2 graphically demonstrates, for the time-independent model, the monotonically rising nature of the concentration-response curve for both all-cause and CVD mortality (vs. a referent HR=1.0 at the mean level of exposure).

A number of sensitivity analyses for alternative models were also conducted (Table 3). In general, associations were stronger and p-values were smaller when we did not adjust for census tract-level contextual environmental variables, including the association with respiratory mortality (HR=1.09; 95% CI: 1.02, 1.18). Adding random effects terms to the time independent model yielded very similar results to those without random effects terms. Time-dependent yearly exposure models gave comparable results to the Year 2000 time-independent baseline exposure model for Total Mortality (HR= 1.03; 95% CI: 0.99, 1.05), CVD Mortality (HR=1.11; 95% CI: 1.06,1.16), and Respiratory (HR=1.05; 95% CI: 0.97, 1.15). Limiting the analysis to only the State of California (the state with the largest number of cohort participants) gave similar results to the entire cohort. To assess the extent to which our censoring of those who moved out of the study State/City might have affected the results, we also present overall results for participants without that censoring, retaining those who moved after 2000, finding that it gave similar results to our base model case with censoring (as shown in Table 2). In addition, in a model that simultaneously also included exposure to the gaseous pollutant O_3 along with $PM_{2.5}$, the $PM_{2.5}$ effect estimate was found to be still significant and its CVD mortality effect estimate not statistically different from the model without the addition of O_3, indicating the $PM_{2.5}$ – CVD mortality association to be robust to the addition of O_3

Discussion

In this large prospective cohort study with detailed baseline individual-level risk factor information on study participants (e.g., smoking, body mass index, alcohol use, etc.), we confirmed a monotonically increasing, and statistically significant, relationship between long-term exposure to $PM_{2.5}$ air pollution and both all-cause and CVD mortality, even at the decreased $PM_{2.5}$ levels experienced in the US since 2000. Comparisons by sex, age, and education for this

cohort did not indicate statistically significant differences in the mortality – $PM_{2.5}$ association across categories.

By finding significant overall associations with all-cause and cardiovascular mortality, the results presented here are consistent with many, but not all, of the prior published results examining $PM_{2.5}$ and mortality. We estimated a 3% increase (95% confidence interval 0–5%) in all-cause mortality for a 10 $\mu g/m^3$ annual increase in $PM_{2.5}$ that, while statistically significant in this large cohort, is lower than many other past estimates. For example, a recent literature review reported a pooled effect estimate of 6% per 10 ug/m^3 $PM_{2.5}$ (95% confidence interval 4–8%) for all-cause mortality (Hoek et al. 2013). Our overall estimate for CVD mortality (10 percent effect per 10 $\mu g/m^3$, 95% confidence interval 5 to15%), agrees more closely with the pooled estimate for CVD mortality reported by Hoek et al. (2013) (11% per 10 $\mu g/m^3$; 95% CI: 6, 16%).

Comparisons with the ACS Cohort, a similarly large nationwide cohort, provides an opportunity to evaluate the issue of association consistency over time in the US. While participants in the ACS Cohort (Pope et al. 2002) were somewhat younger (mean 56 at recruitment, vs. mean 65 in the NIH AARP cohort in 2000), and were exposed during that study's follow up to pollution at an earlier period of time (when the mix of air pollution sources was likely different), it has a similar racial (>90% white) and educational (>50% post-HS education) composition, is of similar size (more than 500,000 participants), and also spans the US, making it probably the most similar US cohort for comparison here. The ACS Cohort reported that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 4% increase in all-cause mortality (95% CI: 1, 8%) (Pope et al. 2002), which is consistent with the corresponding estimate from the present analysis (3% per 10 $\mu g/m^3$; 95% CI: 0, 5%) as shown in Figure 3..

Moreover, the $PM_{2.5}$ - CVD mortality effect estimate reported for the ACS Cohort (12% per 10 $\mu g/m^3$; 95% CI: 8, 15%) (Pope et al. 2004) is very similar to the corresponding association in the NIH AARP cohort (10% per 10 $\mu g/m^3$; 95% CI: 5, 15%) (Figure 3).. This new prospective cohort study's follow up begins at approximately the time that most of the published ACS cohort's follow up analyses ended, providing an independent test as to whether the effects continue to the lower $PM_{2.5}$ levels in the 21st Century. The ACS Study started in 1982 with follow up through 1998, with an annual $PM_{2.5}$ study period mean = 17.7 $\mu g/m^3$ (SD = 3.7) (Pope et al, 2002), while this new NIH-AARP analysis started in 2000 with much lower study follow-up mean $PM_{2.5}$ of 12.2 $\mu g/m^3$ (SD = 3.4) through 2008, and this study therefore documents that for the first time that the $PM_{2.5}$ mortality effects still occur at the much lower post-2000 levels of exposures across the US. In California, the ACS follow-up ended with a mean 1998-2002 $PM_{2.5}$ concentration of 14.1 $\mu g/m^3$ (Jerrett et al, 2013), vs. a much lower end of follow-up mean 2008 $PM_{2.5}$ concentration of 10.4 $\mu g/m^3$ in this work. Figure 3 provides comparative plots of these two cohort's $PM_{2.5}$ mortality estimates across mortality outcomes, for both the US and the State of California (Jerrett et al. 2013; Krewski et al. 2009; Pope et al. 2002; Pope et al. 2004), indicating consistency in their effect estimates, despite the notable decline in pollution levels after 2000.

We have also considered and compared effect estimates per 10 $\mu g/m^3$ $PM_{2.5}$ as a function of alternative $PM_{2.5}$ exposure metrics. In addition to the Year 2000 base $PM_{2.5}$ exposure index, we also considered time-dependent annual mean exposure models for each mortality outcome that directly addressed the declining concentration levels of $PM_{2.5}$ exposures during follow-up. The fixed exposure model has the advantage that it provides results using methods directly comparable to those used in many past such analyses (e.g., the ACS CP-II cohort). We found that the annual mean model yielded results consistent with the baseline (Year 2000) exposure

time-independent model. Lepule et al (2012) also found that varying the exposure metric choice had little effect on $PM_{2.5}$ effect estimates in their analysis of the Harvard Six Cities Study cohort. Not censoring those participants who moved out of the study areas between 2000 and 2006 (n = 28,923) had little effect on these results. We also compared the results using both PMSA and Census-tract level mean exposure metrics, finding similar and confirmatory results with either approach. This may suggest that the fact that people are mobile, and often do not stay at their home residence all day, may limit the exposure assessment accuracy gain derived from knowing home residence locale vs. an area-wide average. Overall, we found that the $PM_{2.5}$ mortality associations in this work are robust to various $PM_{2.5}$ exposure modeling choices.

Numerous past long-term $PM_{2.5}$ –mortality analyses have found higher relative risks among those with less education. For example, Krewski et al. (2000), in their reanalysis of the Six Cities and ACS Cohorts, found that the relative risk of mortality associated with fine particles was greater among individuals with high school education or less, compared to those with more than high school education in the 6-Cities Study, and that the fine particle air pollution mortality risk decreased significantly ($P < 0.05$) with increasing educational attainment in the ACS Cohort. They concluded that "it is possible that educational attainment is a marker for socioeconomic status, which in turn may be correlated with exposure to fine particle air pollution". Similarly, Brunekreef et al. (2009) found in their NLCS-AIR cohort examination of long-term exposure to traffic air pollution that associations with mortality tended to be stronger in case-cohort participants with lower levels of education, but that differences between strata were not statistically significant. Ostro et al. (2009) also estimated stronger associations with components of $PM_{2.5}$ among individuals with lower educational attainment, attributing this trend to the effects of lower socio-economic status. However, no such trend was found in this NIH-

AARP Cohort. This may be because the reported annual incomes of this cohort did not vary with $PM_{2.5}$ concentration (Table 1). Indeed, while the association of education with median income in this cohort was strong (r =0.49), the correlation between $PM_{2.5}$ and median income was much lower (p = 0.03). Thus, it may be that the lack of a strong socio-economic – $PM_{2.5}$ co-variation in this cohort is the reason we did not see the mortality effect modification by education status found in past studies.

This study has both strengths and limitations relative to past such studies. One strength is that we have employed estimates of $PM_{2.5}$ exposure at the participant residence census tract level, rather than applying the overall county or metropolitan area average-exposure that has been used in some major prior studies (e.g., the Medicare and ACS cohorts, respectively) (Eftim et al. 2008; Krewski et al 2009). In addition, most previous studies have assigned only a single fixed exposure level for each study participant (e.g., at the start of the follow-up), while we have also considered a sensitivity model applying time-varying exposure estimates to address the declining $PM_{2.5}$ exposure levels over time. Another strength of this study is that covariate risk factor were collected at the individual level, but a limitation in this is that this was ascertained only at enrollment, and we could not account for temporal changes in risk factors (e.g., smoking and BMI) during follow up. Another limitation is that, other than knowing if and when participants leave the AARP-NIH cohort study areas, we presently lack information on residence location after those participants moved out of the study region. Despite these limitations, as discussed above, our derived effect estimates were found to be largely consistent with other $PM_{2.5}$ mortality results, notably the ACS cohort study (Pope et al. 2002; Pope et al. 2004), the only prior prospective US cohort study of such size with detailed individual-level risk factor information.

Conclusions

Long-term exposure to $PM_{2.5}$ air pollution was associated with a significant increase in CVD and total non-accidental mortality in the cohort as a whole, as well as with a significant increase in respiratory mortality among never smokers, in a new, large, US cohort having detailed individual level participant data and census tract-level $PM_{2.5}$ exposure information. This independent evaluation of the $PM_{2.5}$ – mortality association, in this new large cohort, was robust to various model specification and $PM_{2.5}$ exposure assessment sensitivity analyses, and has found effect estimates (per 10 $\mu g/m^3$ of $PM_{2.5}$ exposure) that are consistent with past estimates, even at the much lower $PM_{2.5}$ air pollution levels experienced in the US since 2000.

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Table 1.

Selected participant characteristics according to quintile of $PM_{2.5}$ exposure in 2000

[mean ± SD or N (%)]

	$PM_{2.5}$ concentration ($\mu g/m^3$)				
Characteristic	**2.9-10.7**	**10.7-12.6**	**12.6-14.2**	**14.2-15.9**	**15.9-28.0**
N*	103576	103330	103345	103410	103380
Age at 2000	66.1 ± 5.3	65.8 ± (5.4)	65.6 ± (5.4)	65.6 ± (5.4)	65.6 ± (5.4)
Sex					
Male	60996 (58.9)	61716 (59.7)	61541 (59.5)	61076 (59.1)	58053 (56.2)
Female	42580 (41.1)	41614 (40.3)	41804 (40.5)	42334 (40.9)	45327 (43.8)
BMI					
<=18.5	845 (0.8)	817 (0.8)	842 (0.8)	809 (0.8)	860 (0.8)
18.5-25	37390 (36.1)	34657 (33.5)	33316 (32.2)	32861 (31.8)	35545 (34.4)
>25 and <=30	42709 (41.2)	43141 (41.8)	43329 (41.9)	43327 (41.9)	41781 (40.4)
>30 and <=35	14714 (14.2)	15959 (15.4)	16546 (16.0)	16794 (16.2)	15823 (15.3)
>35	5329 (5.1)	6041 (5.8)	6510 (6.3)	6816 (6.6)	6531 (6.3)
Unknown	2589 (2.5)	2715 (2.6)	2802 (2.7)	2803 (2.7)	2840 (2.7)
Smoking Status					
Never smoking	34685 (33.5)	35363 (34.2)	37100 (35.9)	37413 (36.2)	38377 (37.1)
Former, =<1 pack/day	28700 (27.7)	27572 (26.7)	27307 (26.4)	27219 (26.3)	27442 (26.5)
Former, >1 pack/day	23163 (22.4)	22575 (21.8)	21285 (20.6)	20414 (19.7)	19696 (19.1)
Currently, =<1 pack/day	8555 (8.3)	8709 (8.4)	8855 (8.6)	9541 (9.2)	9368 (9.1)
Currently, >1 pack/day	4657 (4.5)	5232 (5.1)	4895 (4.7)	4812 (4.7)	4543 (4.4)
Unknown	3816 (3.7)	3879 (3.8)	3903 (3.8)	4011 (3.9)	3954 (3.8)
Race/Ethnicity					
White	95786 (92.5)	95942 (92.9)	96283 (93.2)	94670 (91.5)	88741 (85.8)

Black	1807 (1.7)	2501 (2.4)	3532 (3.4)	5421 (5.2)	7067 (6.8)
Hispanic	2691 (2.6)	1974 (1.9)	1180 (1.1)	920 (0.9)	3011 (2.9)
Asian	1957 (1.9)	1573 (1.5)	1004 (1.0)	1043 (1.0)	2863 (2.8)
Unknown	1335 (1.3)	1340 (1.3)	1346 (1.3)	1356 (1.3)	1698 (1.6)
Marital status					
Married	71327 (68.9)	72457 (70.1)	72094 (69.8)	70980 (68.6)	65450 (63.3)
Widowed/Divorced/ Separated	26664 (25.7)	25923 (25.1)	25816 (25.0)	26592 (25.7)	30330 (29.3)
Never married	4743 (4.6)	4135 (4.0)	4563 (4.4)	5019 (4.9)	6646 (6.4)
Unknown	842 (0.8)	815 (0.8)	872 (0.8)	819 (0.8)	954 (0.9)
Education					
Less than 11 years	5081 (4.9)	6011 (5.8)	6829 (6.6)	7198 (7.0)	5672 (5.5)
High school completed	17019 (16.4)	19880 (19.2)	22604 (21.9)	24055 (23.3)	17750 (17.2)
Post-high school	9560 (9.2)	10590 (10.2)	10652 (10.3)	10933 (10.6)	8890 (8.6)
Some college	25852 (25.0)	24470 (23.7)	21809 (21.1)	21616 (20.9)	25854 (25.0)
College and post graduate	43103 (41.6)	39343 (38.1)	38347 (37.1)	36498 (35.3)	42001 (40.6)
Unknown	2961 (2.9)	3036 (2.9)	3104 (3.0)	3110 (3.0)	3213 (3.1)
State of Residence					
CA	49086 (47.4)	26087 (25.2)	12303 (11.9)	13238 (12.8)	59495 (57.5)
FL	47001 (45.4)	42769 (41.4)	14647 (14.2)	5851 (5.7)	82 (0.1)
GA	0(0.0)	0(0.0)	0(0.0)	156 (0.2)	14331 (13.9)
LA	265 (0.3)	3717 (3.6)	12150 (11.8)	3295 (3.2)	145 (0.1)
MI	78 (0.1)	1157 (1.1)	3051 (3.0)	15546 (15.0)	6307 (6.1)
NC	156 (0.2)	8022 (7.8)	11596 (11.2)	18402 (17.8)	4583 (4.4)
NJ	4585 (4.4)	14568 (14.1)	29238 (28.3)	14657 (14.2)	2149 (2.1)
PA	2405 (2.3)	7010 (6.8)	20360 (19.7)	32265 (31.2)	16288 (15.8)

Contextual Variables					
Median Income ($)	57399 ± 27037	52980 ± 23695	53453 ± 22793	51280 ± 20502	53746 ± 22979
% High School or less	13.6 ± 9.6	15.5 ± 10.0	15.6 ± 9.7	16.2 ± 9.8	18.0 ± 13.7

* Number of participants in $PM_{2.5}$ quintile, after accounting for missing covariate data.

Table 2. NIH-AARP Cohort time independent Cox model $PM_{2.5}$ mortality hazard ratios (and 95% CI's) per 10 $\mu g/m^3$, by cause and cohort subgroup

	All-cause mortality			Cardiovascular mortality			Respiratory Mortality		
Cohort Subset	HR (95% CI)	N deaths	P int.	HR (95% CI)	N deaths	P int.	HR (95% CI)	N deaths	P int.
All	1.03 (1.00, 1.05)	84404		1.10 (1.05, 1.15)	26009		1.05 (0.98, 1.13)	8397	
Age									
<65	1.00 (0.95, 1.05)	20422		1.09 (0.99, 1.19)	5614		1.00 (0.85, 1.19)	1592	
≥65	1.03 (1.00, 1.06)	63982	0.67	1.10 (1.05, 1.15)	20395	0.97	1.06 (0.98, 1.15)	6805	0.24
Sex									
Males	1.03 (1.00, 1.06)	55685		1.09 (1.04, 1.15)	18200		1.02 (0.93-1.12)	5193	
Females	1.02 (0.98, 1.06)	28719	0.77	1.10 (1.02, 1.19)	7809	0.33	1.10 (0.98, 1.23)	3204	0.73
Age & Sex									
Male: age <65	0.99 (0.94, 1.06)	13117		1.08 (0.97, 1.21)	3975		0.99 (0.80, 1.23)	923	
Male: age ≥65	1.04 (1.01, 1.08)	42568		1.10 (1.03, 1.16)	14225		1.03 (0.92, 1.14)	4270	
Female: age <65	1.01 (0.94, 1.10)	7305		1.11 (0.94, 1.30)	1639		1.01 (0.78, 1.31)	669	
Female: age ≥65	1.02 (0.97, 1.06)	21414	0.88	1.10 (1.01, 1.19)	6170	0.82	1.12 (0.99, 1.28)	2535	0.56
Education									
< High School Education	1.02 (0.97, 1.07)	25886		1.05 (0.97, 1.15)	8176		1.04 (0.91, 1.19)	2900	
High School Education	1.06 (0.98, 1.15)	8668		1.21 (1.05, 1.40)	2708		1.00 (0.79, 1.26)	883	

> High School Education	1.02 (0.99, 1.05)	46577	0.65	1.10 (1.04, 1.16)	14057	0.86	1.07 (0.97-1.18)	4275	0.38
Smoking									
Never Smoked	1.04 (0.99, 1.08)	19785		1.11 (1.02, 1.20)	6384		1.27 (1.03-1.56)	1004	
Former Smoker	1.02 (0.99, 1.06)	44590		1.07 (1.01, 1.14)	13934		1.04 (0.94, 1.14)	4677	
Current Smoker	1.02 (0.95, 1.06)	16354	0.58	1.14 (1.02, 1.25)	4451	0.46	1.01 (0.88, 1.16)	2372	0.70

Table 3. NIH-AARP Cohort $PM_{2.5}$ mortality Hazard Ratios and 95% CI's per 10 $\mu g/m^3$ $PM_{2.5}$ for Alternative Model Specifications

Model	N	All	CVD	Respiratory
Full Baseline Model, Time-Independent 2000 Census Tract Mean $PM_{2.5}$ Exposures	517,041	1.03 (1.00, 1.05)	1.10 (1.05, 1.15)	1.05 (0.98, 1.13)
Full Model, Time-Dependent Annual Census Tract Mean $PM_{2.5}$ Exposures	517,041	1.03 (0.99, 1.05)	1.11 (1.06, 1.16)	1.05 (0.97, 1.15)
Full Baseline Model, 2000 PMSA Mean $PM_{2.5}$ Exposures	474,565	1.01 (0.98, 1.04)	1.10 (1.04, 1.16)	1.06 (0.97, 1.16)
Full Baseline Model w/o Contextual Vars.	517,041	1.06 (1.03, 1.08)	1.15 (1.10, 1.20)	1.09 (1.02, 1.18)
Full Baseline Model with Random Effects	517,041	1.03 (1.00, 1.05)	1.10 (1.05, 1.14)	1.06 (0.99, 1.14)
Full Baseline Model With Ozone	466,121	1.02 (0.99, 1.05)	1.07 (1.02, 1.12)	1.02 (0.94, 1.11)
Full Baseline Model Retaining All Who Moved From Study Area After 2000	517,041	1.02 (1.00, 1.05)	1.10 (1.06, 1.15)	1.04 (0.97, 1.12)
Full Baseline Model for California Only	160,209	1.02 (0.99, 1.04)	1.10 (1.05, 1.16)	1.01 (0.93, 1.10)

Figure Legends

Figure 1. Continental U.S. Map of NIH-AARP Study Participants' Census Tracts

Figure 2. Concentration–response curves (solid lines) and 95% CIs (dashed lines) based on natural spline (ns) models with 4 df, standard Cox models stratified by age and sex, adjusted for all individual-level covariates (race, education, marital status, BMI, alcohol consumption, and smoking history) and contextual covariates (Median Income ($), and % High School or less) for: (*A*) All Non-accidental causes, (*B*) Cardiovascular disease. The tick marks on the *x*-axis identify the distribution of observations according to $PM_{2.5}$ concentrations.

Figure 3. Comparison of NIH-AARP Cohort vs. published ACS Cohort All-Cause and By-Cause mortality Hazard Ratios per 10 $\mu g/m^3$ $PM_{2.5}$, with 95%ile CI's, for the State of California (CA) and nationwide (US) (Jerrett et al. 2013; Krewski et al. 2009).

Figure 1.

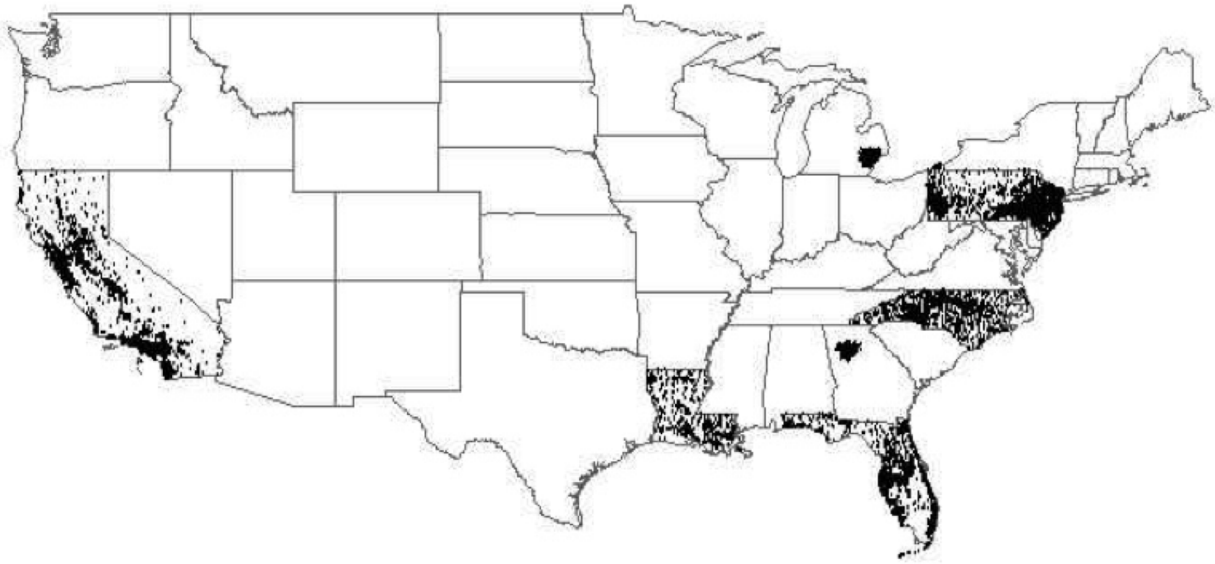


Figure 2.

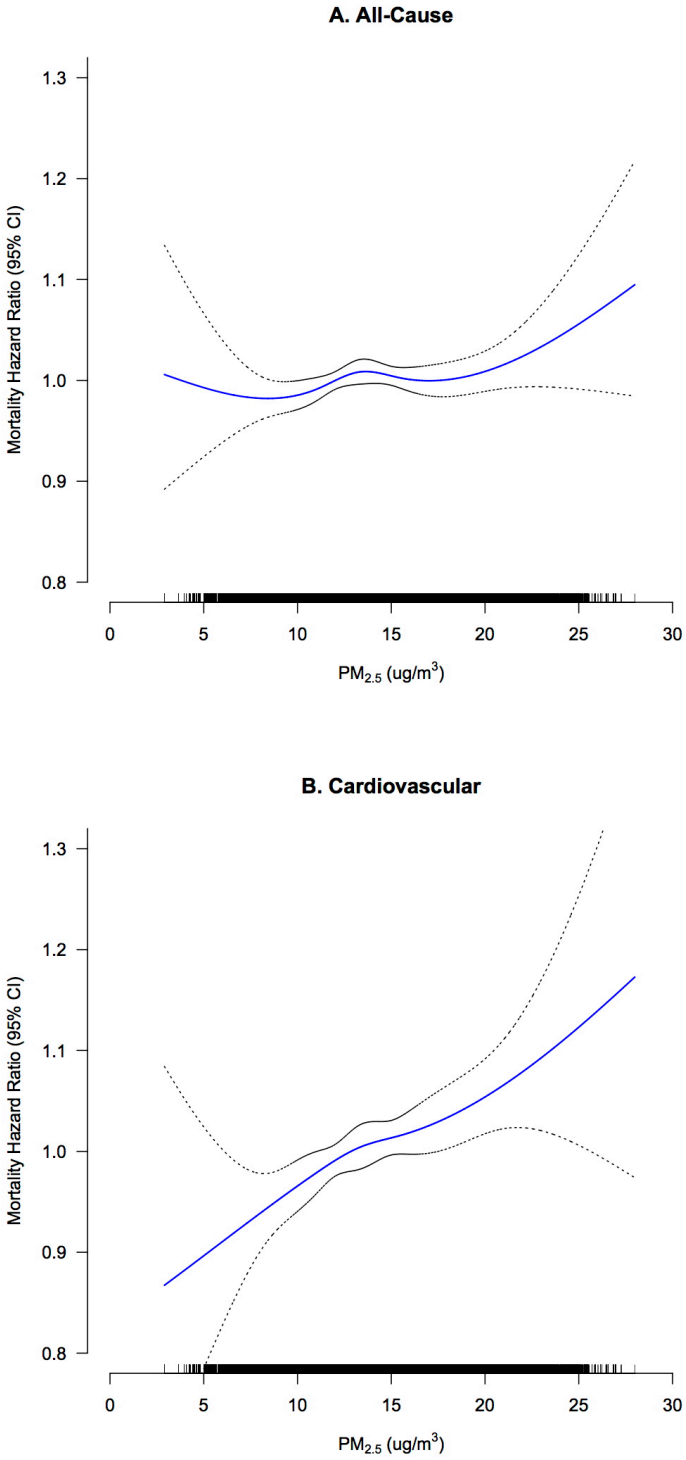
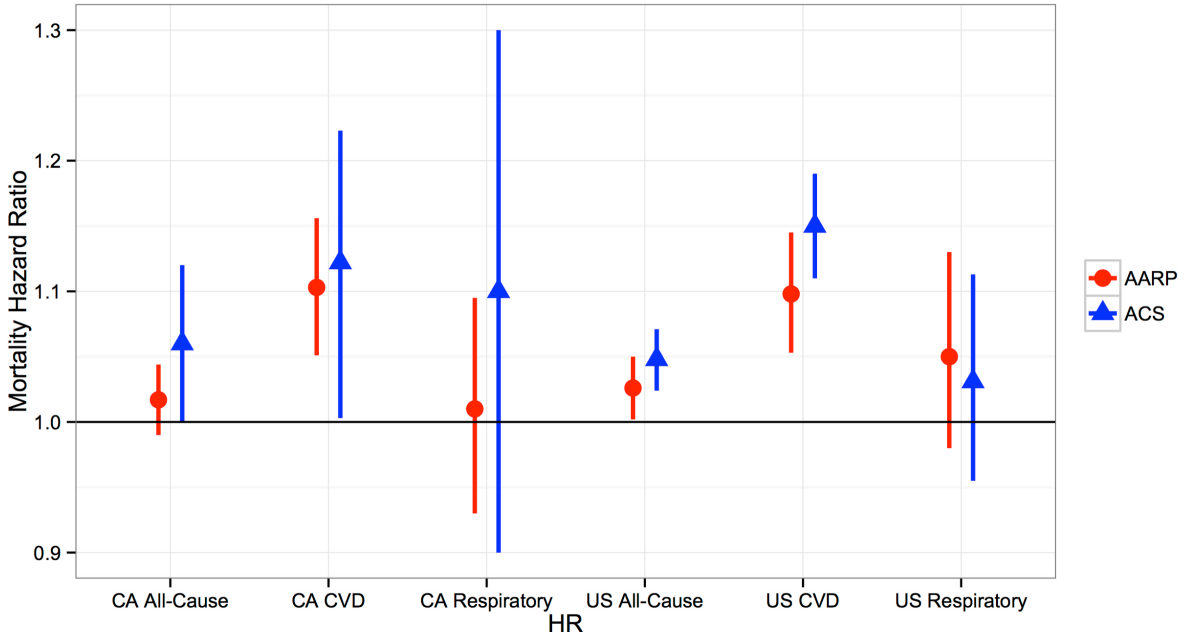

A. All-Cause
Mortality Hazard Ratio (95% CI)
1.3
1.2
1.1
1.0
0.9
0.8
0
5
10
15
20
25
30
PM2.5 (ug/m3)
B. Cardiovascular
Mortality Hazard Ratio (95% CI)
1.3
1.2
1.1
1.0
0.9
0.8
0
5
10
15
20
25
30
PM2.5 (ug/m3)

Figure 3.


1.3
1.2
1.1
1.0
0.9
Mortality Hazard Ratio
CA All-Cause
CA CVD
CA Respiratory
US All-Cause
US CVD
US Respiratory
HR
AARP
ACS